1611 Health-Related Quality of Life Outcomes in Patients with Myelodysplastic Syndromes with Ring Sideroblasts Treated with Luspatercept in the MEDALIST Study

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Introduction

Patients with myelodysplastic syndromes (MDS) experience severe anemia, which is commonly managed with frequent red blood cell transfusions (RBCT) in patients refractory to erythropoiesis-stimulating agents. At diagnosis, 85% of patients have anemia and 30–50% depend on RBCT. The administration of RBCT itself provides transient relief in anemia-related symptoms. Per protocol, MEDALIST investigators were advised to transfuse for symptoms related to anemia at the investigators' discretion. Hence, cessation or reduction of RBCT may increase anemia-related symptoms and negatively impact health-related quality of life (HRQoL). Luspatercept is a first-in-class erythroid maturation agent providing clinically meaningful reduction in transfusion burden in patients with transfusion-dependent anemia due to Revised International Prognostic Scoring System (IPSS-R)-defined Very low-, Low-, or Intermediate-risk MDS with ring sideroblasts in the phase 3 MEDALIST trial (NCT02631070). However, the impact of luspatercept on patients' HRQoL has not been evaluated. This analysis aimed to evaluate the effect of luspatercept versus placebo on HRQoL of patients treated for MDS from baseline through Week 25 of the MEDALIST study.

Methods

Patients received luspatercept or placebo every 3 weeks for 24 weeks, plus best supportive care (BSC), including tailored amounts of RBCT. Effects of luspatercept versus placebo on HRQoL were evaluated as secondary and exploratory endpoints in the MEDALIST study. In the primary analysis, mean change from baseline to Week 25 (clinical assessment visit) in the European Organisation for Research and Treatment of Cancer's core quality of life questionnaire, version 3.0 (EORTC QLQ-C30) and in the QoL assessment in MDS questionnaire (QOL-E) was determined using mixed-effects repeated measures analysis. Clinically meaningful change within each treatment arm was defined as a ≥ 10-point change in patient-reported outcome (PRO) score from baseline for all EORTC QLQ-C30 domains, and ≥ 0.5 standard deviation of the baseline domain score for all QOL-E domains. Differences between luspatercept and placebo were considered clinically meaningful if the change from baseline between treatment arms exceeded the threshold for a clinically meaningful difference. In an exploratory analysis, patient-reported impact of transfusion dependence and overall side effects on their daily life was estimated using the QOL-E instrument.

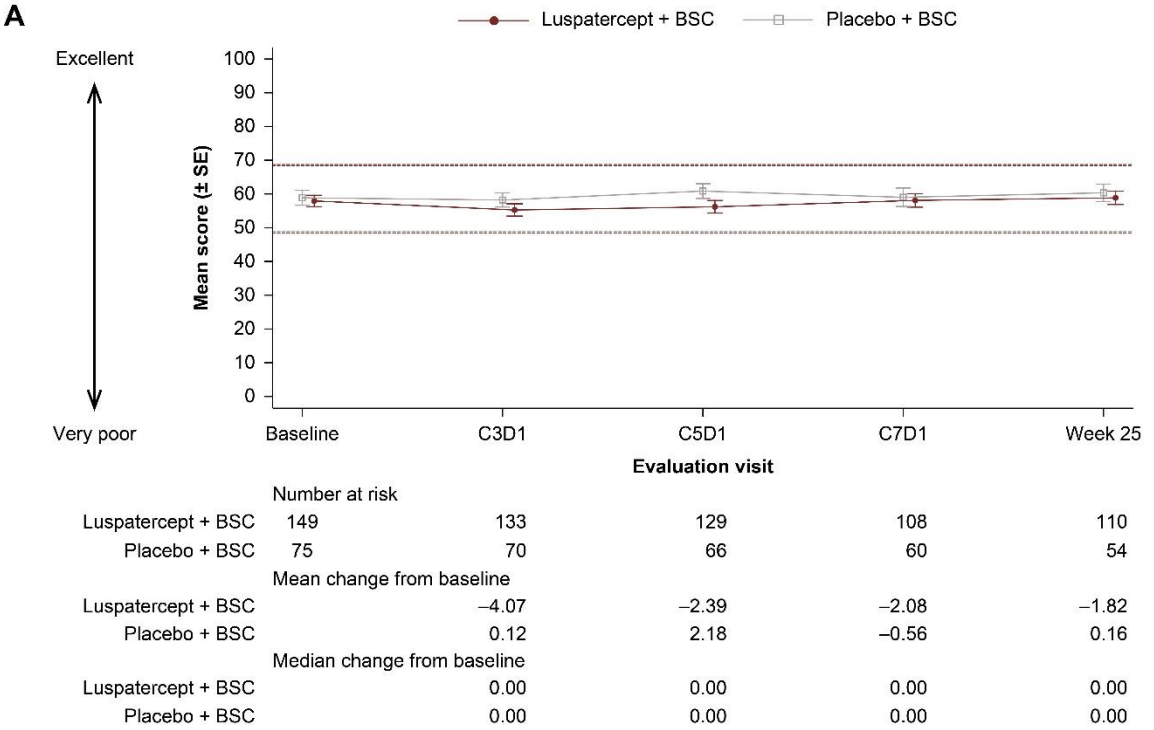
Results

A total of 229 patients were randomized; 153 patients to luspatercept and 76 to placebo. The HRQoL-evaluable population, consisting of patients with ≥ 1 post-baseline HRQoL score, was 149 patients in the luspatercept arm and 76 patients in the placebo arm. Questionnaire compliance rates among patients remaining on treatment were similar between luspatercept and placebo treatment groups at Week 25 (EORTC QLQ-C30, 88.2% vs 79.4% and QOL-E, 72.5% vs 69.7%). At baseline, MEDALIST patients had a clinically meaningfully worse HRQoL compared with the general population in 5 of 15 EORTC QLQ-C30 domains: physical functioning, role functioning, social functioning, fatigue, and dyspnea. Through Week 25, there was no clinically meaningful difference in change from baseline between and within the luspatercept and placebo arms across all EORTC QLQ-C30 (Global health status shown in Figure A) and QOL-E domains. A greater proportion of patients in the luspatercept arm relative to placebo reported improvements in daily life from the impact of transfusion burden (Figure B). Relative to baseline, the proportion of patients reporting a lower impact of transfusion dependence on their daily life was 39% versus 22% in luspatercept versus placebo at Week 25; in contrast, the proportion of patients reporting a higher impact of transfusion dependence on their daily life was 12% versus 22% in luspatercept versus placebo. Impact of treatment side effects on patients was comparable between luspatercept and placebo.

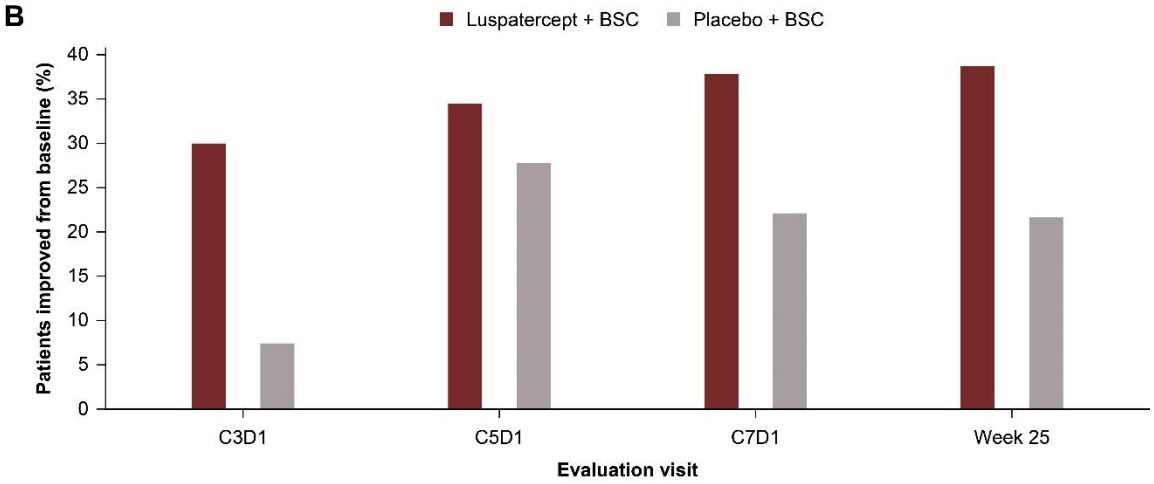
Conclusions

Luspatercept with BSC reduced RBCT burden and patient-reported transfusion impact on their daily life, while maintaining other aspects of HRQoL from baseline through Week 25 in the MEDALIST study.

Figure. Patient-reported (A) mean Global health status/QoL score over time on the EORTC QLQ-C30 and (B) transfusion burden on QOL-E[a] from treatment initiation through Week 25



Number at risk					
Luspatercept + BSC	149	133	129	108	110
Placebo + BSC	75	70	66	60	54
Mean change from baseline					
Luspatercept + BSC		–4.07	–2.39	–2.08	–1.82
Placebo + BSC		0.12	2.18	–0.56	0.16
Median change from baseline					
Luspatercept + BSC		0.00	0.00	0.00	0.00
Placebo + BSC		0.00	0.00	0.00	0.00



	C3D1		C5D1		C7D1		Week 25	
	Luspatercept	**Placebo**	**Luspatercept**	**Placebo**	**Luspatercept**	**Placebo**	**Luspatercept**	**Placebo**
N	127	68	122	65	106	59	106	51
Improved, %	30	7	34	28	38	22	39	22
Stable, %	59	74	49	52	47	59	49	57
Worsening 1, %	9	13	15	17	14	17	10	20
Worsening 2, %	2	6	2	3	1	2	2	2

[a]Question from the PRO instrument: What effect of the disease disturbs your daily life? A. Being dependent on transfusions (response options: "No, not at all", "A little bit", and "Yes, extremely")
BSC, best supportive care; C3D1, Cycle 3 Day 1; C5D1, Cycle 5 Day 1; C7D1, Cycle 7 Day 1; SE, standard error

2190 Effect of Luspatercept on Biomarkers of Erythropoiesis in Patients (Pts) with Lower-Risk Myelodysplastic Syndromes (LR-MDS) in the Medalist Trial

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Introduction

LR-MDS are characterized by ineffective erythropoiesis that leads to anemia and red blood cell (RBC) transfusion dependence. Luspatercept is a first-in-class erythroid maturation agent that binds to select TGF-β superfamily ligands and enhances late-stage erythropoiesis. MEDALIST is a phase 3, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of luspatercept in pts with LR-MDS (IPSS-R-defined Very low-, Low-, and Intermediate-risk) with ring sideroblasts who required RBC transfusions and were ineligible for, intolerant of, or refractory to erythropoiesis-stimulating agents. Clinical benefit (CB; defined as RBC transfusion independence [RBC-TI] ≥ 8 weeks and/or modified hematologic improvement-erythroid [mHI-E] per IWG 2006 criteria) in the primary MEDALIST treatment phase (Weeks 1-24) was achieved by 58.2% of pts in the luspatercept arm and 21.1% in the placebo arm ($P < 0.0001$). The objective of the study was to investigate the effect of luspatercept treatment on erythropoiesis biomarkers and their relationship to CB in the primary MEDALIST treatment phase (Weeks 1-24).

Methods

In the MEDALIST trial, 229 pts were randomized to receive either luspatercept (N = 153) or placebo (N = 76). Reticulocyte count was determined in blood samples collected at baseline and during the primary treatment phase. Serum biomarkers (soluble transferrin receptor 1 [sTfR1],

erythroferrone [ERFE], and erythropoietin [EPO]) were measured by ELISA. Bone marrow (BM) erythroid precursors (EP) were determined by cytomorphology from BM aspirates. Biomarker levels were compared between baseline and Week 25 within treatment arms and between pts with CB and without CB in the luspatercept arm using a paired 2-tailed t-test and unpaired t-test (parametric method).

Results

In the luspatercept arm, mean reticulocyte count increased from baseline, starting at 8 days after first dose (55.1 vs 34.5 $\times$ 10^9/L at baseline, $P < 0.0001$), and remained elevated throughout the evaluation period (Figure). Mean EPO levels increased significantly within 6 weeks after first dose (440.1 vs 220.4 IU/L at baseline, $P < 0.0001$) and remained elevated up to Week 25. Similarly, levels of sTfR1 ($P < 0.0001$), ERFE ($P < 0.0001$), and EP ($P = 0.0010$) were elevated at Week 25 relative to baseline (Table). The mean transfusion burden (within 16 weeks) was significantly reduced at Week 25 compared with baseline (7.2 vs 11.0 units, $P < 0.0001$).

In contrast, in the placebo arm, reticulocyte count, EPO levels, and 16-week transfusion burden remained largely unchanged, while levels of sTfR1 ($P < 0.0001$), ERFE ($P = 0.0431$), and EP ($P = 0.0010$) were significantly lower at Week 25 relative to baseline.

In the luspatercept arm, mean baseline EP were higher in 87 pts with CB (31.3%) compared with 63 pts without CB (26.5%; $P = 0.0298$). No statistically significant differences in baseline EPO, ERFE, sTfR1, reticulocyte count, and 16-week transfusion burden were observed in either group. At Week 25, pts with luspatercept and CB had a significantly greater increase of reticulocyte count (2.7 vs 1.8 mean fold increase from baseline, $P = 0.0017$), but not EPO levels (2.9 vs 4.3 mean fold increase from baseline, $P = 0.1370$) compared with pts without CB. Changes in erythropoiesis-related biomarkers (EP, ERFE, and sTfR1) did not differ significantly between pts with and without CB.

To investigate whether luspatercept affects erythroid maturation, the ratio of reticulocyte/sTfR1 was calculated. This ratio was reasoned to be an approximation of the ratio of late-stage erythropoiesis (reticulocytes) within total erythropoiesis (sTfR1). Luspatercept increased the mean ratio of reticulocyte/sTfR1 in pts with CB (2.2 in Week 25 vs 1.5 at baseline, $P < 0.0001$) and no CB (1.9 in week 25 vs 1.3 at baseline, $P = 0.0071$).

Conclusions

Luspatercept-treated pts in the MEDALIST trial had an increase of erythropoiesis-associated biomarkers. Luspatercept-mediated CB (RBC-TI $\geq$ 8 weeks and/or mHI-E) was associated with increased blood reticulocyte counts and was higher in pts with expanded BM erythropoiesis (as measured by EP) at baseline. Together with the observation that the ratio of reticulocytes/sTfR1 increased during luspatercept treatment, this suggests that the luspatercept mechanism of

efficacy in pts with LR-MDS is associated with an increase of erythroid maturation and reticulocytes.

Table. Erythropoiesis biomarkers in Weeks 1–24 of the MEDALIST trial

	Luspatercept N = 163		*P* value (Week 25 vs baseline)	Placebo N = 78		*P* value (Week 25 vs baseline)
	Baseline	Week 25		Baseline	Week 25	
Blood reticulocyte count mean (n), 10^9/L	34.5 (135)	71.9 (108)	< 0.0001	38.4 (68)	37.3 (58)	0.4891
Serum EPO level, mean (n), IU/L	220.4 (152)	662.9 (120)	< 0.0001	215.5 (74)	243.2 (64)	0.3593
Serum sTfR1 level, mean (n), nM	32.7 (143)	42.8 (125)	< 0.0001	31.6 (74)	23.8 (66)	< 0.0001
Serum ERFE level, mean (n), ng/mL	20.9 (137)	27.0 (122)	< 0.0001	22.9 (68)	22.4 (58)	0.0431
BM EP level, mean (n), %	29.3 (150)	34.3 (130)	0.0010	29.9 (75)	23.4 (66)	0.0010
16-week transfusion burden, mean (n), RBC units	11.0 (153)	7.2 (128)	< 0.0001	11.5 (76)	12.0 (68)	0.4438

BL, baseline; BM, bone marrow; EP, erythroid precursors; EPO, erythropoietin; ERFE, erythroferrone; RBC, red blood cell; sTfR1, soluble transferrin receptor 1.

Figure. Blood reticulocyte count increased early and was sustained in the luspatercept arm